This booklet is intended to help citizens, patients, businesses and students to understand how the European Union (EU) promotes pharmaceutical trade and guarantees the quality, safety, and efficacy of medicinal products on the market in the 15 Member States. It also explains the pharmacovigilance mechanisms and the electronic communications network that have been put in place since the new Community system was established in 1995 to facilitate the dissemination of information on medicinal products, in particular between the Commission and national drug authorities.

Finally, it aims to familiarise those interested in pharmaceuticals and in the European Union with the new pharmaceutical marketing authorisation procedures that came into operation in 1995 and the decisions taken to improve the single market within the EU.

Introduction

Since 1985, a score of Community directives have been adopted with the aim of achieving a single, EU-wide market for pharmaceuticals. This single market should help not only to enhance the quality of life of European citizens, but also strengthen the European pharmaceutical industry’s competitiveness and research capability, for generations to come.

From the first European Community pharmaceutical directive, issued in 1965, to our days, Community lawmakers have striven to ensure that, first and foremost, medicinal products for human use help maintain a high level of protection for public health. Much of the impetus behind Directive 65/65/EEC1 stemmed from determination to prevent a recurrence of the thalidomide disaster in the early 1960s, when thousands of babies were born with limb deformities as a result of their mothers taking thalidomide as a sedative during pregnancy. This experience, which shook public health authorities and the general public, made it clear that to safeguard public health, no medicinal product must ever again be marketed without prior authorisation.

A decade later, two landmark directives, 75/318/EEC2 and 75/319/EEC3, sought to bring the benefits of innovative pharmaceuticals to patients across the European Community, by introducing a procedure for the mutual recognition, by Member States, of their respective national marketing authorisations. To facilitate mutual recognition, Directive 75/319/EEC set up a Committee for Proprietary Medicinal Products (CPMP), which first assessed whether candidate products complied with Directive 65/65/EEC. Subsequent problems in implementing the pharmaceutical directives were examined by the Pharmaceutical Committee, set up by Directive 75/320/EEC. By seeking to ensure the free movement of medicinal products

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1 OJ N° 022, 09/02/1965 p. 0369 - 0373
2 OJ N° L 147, 09/06/1975 p. 1
3 OJ N° L 147, 09/06/1975 p. 13
throughout the Community, in line with Treaty provisions on the free movement of goods, these two directives marked the first step towards creating a Community-wide single market in pharmaceuticals.

From Community to Union - the institutions

The European Economic Community institutions were founded in the aftermath of the Second World War, to bring European nations closer together, and establish an economic basis for peace and stability for the generations to come.

In 50 years, the Community's institutions have grown larger and more numerous, but they still form the constitutional framework within which Member States work towards the ever closer union envisaged by its founders. In the early years, the Commission would propose, the European Parliament would advise, the Council of Ministers would decide and the Court of Justice would interpret. However, the European Single Act (1986*), the Maastricht Treaty on European Union (1992*), and the Treaty of Amsterdam of (1997*), have changed the way they work, and extended their remit beyond purely economic matters to encompass public health, social policy, research, and consumer and environment protection.

The 1957 Treaty of Rome empowered the European Parliament only to deliver opinions on European Commission proposals for legislation, under the "consultation" procedure. Decisions were taken by the Council of Ministers, which was not obliged to take these opinions into account.

The 1986 Single European Act gave Parliament more say in the drafting of Community legislation, by introducing the “co-operation procedure”. However, the Council still had the final word.

Under the "co-decision" procedure, incorporated in the Treaty in Maastricht and revised in Amsterdam, no draft text can become law without the formal agreement of both the European Parliament and the Council. In other words, as far as the procedure is concerned, these two institutions are now on an equal footing.

The Treaty of Amsterdam, which entered into force on 1 May 1999, thus made some significant institutional changes. Here are some examples.

- The role of the European Parliament, as a genuine co-legislator with the Council, was recognized by streamlining the co-decision procedure and extending the areas to which it applies. Overall, the number of procedures by which Parliament helps to shape legislation was reduced to three, i.e. co-decision, assent and consultation. Parliament was also empowered to make proposals for its own electoral procedure, based on principles common to all Member States.

- The areas in which the Council of Ministers takes decisions by a qualified majority voting was also extended, which should facilitate decision-making.

*Dates of signature
• A more effective and efficient Commission, which plays a central role in the institutional structure as initiator, administrator, mediator, negotiator and guardian of the Treaties, will be achieved by:

- giving the Commission President greater powers in selecting Commissioners and exercising policy leadership;

- improving the Commission's internal organisation and the structuring of its departments;

- ensuring that, as the Community enlarges, the composition of the Commission will evolve.

• The powers of the Court of Justice have been extended and clarified as regards safeguarding fundamental rights, action by the Union on asylum and immigration, and cooperation in police and judicial matters.
**Aims and tasks of the Unit responsible for pharmaceuticals**

The pharmaceutical sector is extensively regulated in the dual interest of protecting public health while completing the single market for pharmaceuticals. The European market in pharmaceuticals is the largest in the world, and sets the international benchmark for production and export volumes.

The aims of the Unit, which is part of the Enterprise Directorate-General, are to:

- ensure a high level of protection of public health;
- bring about a single market in pharmaceuticals;
- foster a stable and predictable environment for pharmaceutical innovation.

The Unit's tasks, under the authority of the Commissioner responsible, are to:

**Regulatory policy**

- maintain, update and simplify EU pharmaceutical legislation whenever feasible;
- draft new legislation;
- support the mutual recognition of national marketing authorisation decisions;
- ensure appropriate standards of consumer protection in respect of pharmaceuticals;
- provide guidance on pharmaceutical legislation and ensure that it is properly implemented within the EU.

**Decision-making process**

The Unit assists the decision-making process by:

- proposing Commission decisions for the authorisation and surveillance of medicinal products;
- proposing Commission regulations on maximum residue limits (MRLs) of veterinary medicinal products in foodstuffs of animal origin;
- drawing up detailed guidance for the application of Community procedures.

**Industrial policy**
The Unit's industrial policy aim is to support pharmaceutical innovation in the European Union and to foster competition and transparency in the Community pharmaceutical market.

External policy

The Unit's external policy tasks are to:

- promote international harmonisation within ICH\(^4\), VICH\(^5\) and the European Pharmacopoeia;
- negotiate mutual recognition agreements with third countries;
- pursue co-operation with Central and Eastern European Countries (CEECs);
- prepare for and verify the implementation of EC pharmaceutical legislation in EU accession candidate countries.

Information technology

The Unit's information technology tasks are to:

- promote collaboration between pharmaceutical regulatory bodies in Europe by establishing telematic networks, tracking systems and databases on pharmacovigilance and prices;
- facilitate the dissemination of information within the industry and to citizens.

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\(^4\) International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use

\(^5\) International Conference on Harmonisation of technical requirements for registration of veterinary medicinal products
**Key aims of the Enterprise DG**

The key aims of the European Commission's Enterprise Directorate-General are:

- promoting entrepreneurship and a dynamic enterprise culture;

- improving the enterprise environment, including the legislative and financial framework, and the access to finance;

- enhancing the competitiveness of European enterprises, for instance through methods of benchmarking and best practice and concerted actions with the Member States;

- upgrading the role of services in the European economy, taking into account their potential in job creation, especially by promoting electronic commerce, information technology and support services for enterprises;

- promoting innovation and the ability of European enterprises to use the results of research and bring it to the market in the form of new products and services;

- enabling enterprises to take full advantage of the Single Market, including, where appropriate, the completion of legislation and standards and, in particular, the simplification of legislation at EU and national levels;

- encouraging European enterprises to fully use the opportunities created by globalisation, and promoting their legitimate interests in the global market by ensuring free access to markets and a level playing field;

- integrating the enterprise and competitiveness dimensions in other Community policies, such as competition, environment, regional, research and trade policies.
The new procedures for evaluating medicinal products and granting marketing authorisations

A new European system for authorising medicinal products since January 1995

The new European system offers two routes for authorising medicinal products:

- a "centralised" procedure, with applications made directly to the European Agency for the Evaluation of Medicinal Products (commonly known as the European Medicines Evaluation Agency - EMEA) leading to the grant of a European marketing authorisation by the Commission. Use of this procedure is compulsory for products derived from biotechnology, and optional for other innovative medicinal products;

- a "mutual recognition" procedure, which is applicable to the majority of conventional medicinal products. Applications are made to the Member States selected by the applicant and the procedure operates by mutual recognition of national marketing authorisations. Where this is not possible, the EMEA is called upon to prepare a binding arbitration. Purely national authorisations are still available for medicinal products to be marketed in one Member State.

The EMEA was established in 1995, partly in response to demands from consumers' organisations, particularly the BEUC (Bureau Européen des Consommateurs) and the European Parliament. It was founded to enable Community institutions to discharge their considerable responsibilities resulting from the introduction of two new marketing authorisation procedures and other tasks, all of which will be explained in this chapter. The EMEA’s main task is to co-ordinate the scientific evaluation of the safety, efficacy and quality of medicinal products which undergo either procedure. All scientific questions arising in these procedures are dealt by the EMEA.

The day-to-day management of the Agency is entrusted to its Executive Director, under the supervision of a Management Board. The Board consists of two representatives from each Member State, two representatives of the European Commission and two representatives appointed by the European Parliament.

(The EMEA's website address is http://www2.eudra.org).

EMEA aims

The EMEA's key aims are to:

- protect and promote public health by providing safe and effective medicines for human and veterinary use;

- give patients quick assess to innovative new therapy;

- facilitate the free movement of pharmaceutical products throughout the EU;
- improve information for patients and professionals on the correct use of medicinal products, to improve animal health;

- protect consumers of animal products and harmonise scientific requirements in order to optimise pharmaceutical research worldwide.

**EMEA tasks**

The EMEA's key tasks are to:

- provide Member States and Community institutions with the best possible scientific advice on questions about the quality, safety and efficacy of medicinal products for human and veterinary use;

- establish a pool of multinational scientific expertise (by mobilising existing national resources) in order to achieve a single evaluation via the centralised or mutual recognition marketing authorisation procedures;

- organise speedy, transparent and efficient procedures for the authorisation, surveillance and where appropriate, withdrawal of medicinal products in the EU;

- advise companies on the conduct of pharmaceutical research;

- reinforce the supervision of existing medicinal products (by co-ordinating national pharmacovigilance and inspection activities);

- create databases and electronic communication facilities as necessary to promote the rational use of medicines.

In 1993, the Council of Ministers approved two new procedures for the authorisation of medicinal products, to ensure that they could quickly be made available to citizens across the European Union: the **centralised** and **mutual recognition** procedures.

**1. The centralised procedure**


The centralised procedure, which came into operation in 1995, allows applicants to obtain a marketing authorisation that is valid throughout the EU. It is compulsory for medicinal products manufactured using biotechnological processes, but may also be used for other innovative products, on a voluntary basis.

⁶ Official Journal L 214, 24/08/1993 p. 0001-0002
⁷ Official Journal L 214, 24/08/1993 p. 40
When a company wishes to place a medicinal product that is eligible for the centralised procedure on the market, it sends an application directly to the Agency, to be assessed by the Committee for Proprietary Medicinal Products (CPMP) or Committee for Veterinary Medicinal Products (CVMP). Both the CPMP and the CVMP meet every month.

The procedure results in a Commission decision, which is binding on all EU Member States, to authorise the product. Centrally-authorised products may be marketed in all Member States.

What happens once the pharmaceutical company has submitted its application?

Full copies of the marketing authorisation application file are sent to a rapporteur and a co-rapporteur designated by the competent EMEA scientific committee. They co-ordinate the EMEA's assessment of the medicinal product and prepare draft reports.

Once the draft reports are prepared (other experts might be called upon for this purpose), they are sent to the CPMP or CVMP, whose comments or objections are communicated to the applicant. The rapporteur is therefore the privileged interlocutor of the applicant and continues to play this role, even after marketing authorisation has been granted.

The rapporteur and co-rapporteur then assess the applicant's replies, submit them for discussion to the CPMP or CVMP and, taking into account the conclusions of this debate, prepare a final assessment report which also includes the draft summary of product characteristics, the patient package leaflet and the texts proposed for the various packaging materials.

Once the evaluation is completed, the CPMP gives a favourable or unfavourable opinion as to whether to grant the authorisation.

The time limit for the evaluation procedure is 210 days.\(^8\)

The Agency then has thirty days to forward its opinion to the Commission. This is the start of the second phase of the procedure: the decision-making process. The Agency sends the Pharmaceutical Unit its opinion in the eleven Community languages, with annexes containing:

- the summary of product characteristics (Annex 1);
- the particulars of the manufacturing authorisation holder responsible for batch release, the particulars of and the manufacturer of the biological active substance and the conditions of the marketing authorisation (Annex 2);
- the labelling and the package leaflet (Annex 3).

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\(^8\) The application formalities and the detailed procedure are described in the Notice to Applicants. The Notice to Applicants is available in the Eudralex volumes http://pharmacos.eudra.org.
During the decision-making process, the Commission services check that the marketing authorisation complies with Community law and turn the Agency opinion into a binding decision for all the Member States.

The Commission has thirty days to prepare a draft decision. The medicinal product is assigned a Community registration number, which will be placed on its packaging if the marketing authorisation is granted. During this period, various Commission directorates-general are consulted on the draft marketing authorisation decision. They have ten days to deliver their opinions.

The draft decision is then sent to the Standing Committee on Medicinal Products for Human Use, or the Standing Committee on Veterinary Medicinal Products (Member States have one representative each in both of these committees) for their opinions.

Member States have fifteen days to return their linguistic comments and thirty days for scientific and technical ones. This procedure is conducted in writing but if a duly justified objection is raised by one or more Member States, the committee holds a plenary meeting to discuss it.

When the opinion is favourable, the draft decision is forwarded to the Commission Secretariat-general for adoption through an habilitation procedure, enabling the Commissioner for Enterprise and the Information Society to issue the final decision.

When the decision is approved, the Commission Secretariat-General notifies the Member States and the marketing authorisation holder in their respective languages. The decision is then published in the Official Journal of the European Communities.

Marketing authorisations granted via the centralised procedure are valid for five years. Applications for extension must be made to EMEA three months before this five-year period expires.
A popular procedure

The number of centralised marketing authorisations granted has grown steadily since 1995. To date 122 medicinal products have been authorised through this procedure.

The number of Commission decisions issued concerning medicinal products (including Commission decisions amending marketing authorisations already granted) grows each year, as indicated in the following figure. In 1999, more than 200 Commission Decisions have been issued in one language.

![Number of Commission Decisions per year concerning marketing authorisations issued since 1995](image)

2. The mutual recognition procedure

Basic arrangements for implementing the mutual recognition procedure laid down in Council Directive 93/39/EEC\(^9\) have been made in all Member States, in accordance with Council Directives 65/65/EEC\(^10\) and 75/319/EEC\(^11\). To be eligible for this procedure, a medicinal product must already have been authorised for marketing in one Member State, and sufficient data on it must be available.

Since 1 January 1998, the mutual recognition procedure has been compulsory for all medicinal products to be marketed in a Member State other than that in which they were first authorised. Any national marketing authorisation granted by an EU Member State's national authorities can be used to support an application for its mutual recognition by other Member States.

How does the mutual recognition procedure work?

The mutual recognition procedure works on the principle of the mutual recognition by EU Member States of their respective national marketing authorisations. An

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\(^9\) Official Journal N° L 015, 17/01/1987 p. 0038 - 0041

\(^10\) Official Journal N° 022, 9/02/1965, p. 0369-0373

\(^11\) Official Journal N° L 147, 9/06/1975, p.0013-0022
application for recognition may be addressed to one or more Member States. The applications submitted must be identical and all Member States must be notified of them. As soon as one Member State decides to evaluate the medicinal product (at which point it becomes the "Reference Member State"), it notifies this decision to other Member States ("Concerned Member States"), to whom applications have also been submitted. Concerned Member States may then suspend their own evaluations, and await the Reference Member State's detailed assessment report on the product. As soon as the assessment is completed, copies of this report are sent to all Member States and they then have 90 days to recognise the decision of the Reference Member State and the SPC as approved by it (by granting a marketing authorisation with an identical SPC). Should any Member State refuse to recognise the original national authorisation, e.g. on public health grounds, are submitted to the appropriate EMEA scientific committee (CPMP or CVMP, as appropriate), for arbitration.

The EMEA committee opinion is then forwarded to the Commission, for the start of the decision making process. As in the centralised procedure, this process entails consulting various Commission directorates-general and the regulatory standing committees on human or veterinary medicinal products, as appropriate.

Once the Commission decision is taken, it is binding on all the Member States concerned, which must withdraw, grant, or vary the marketing authorisations as necessary to comply with the decision. Other Member States not directly concerned at the time of the decision are also bound as soon as they receive a marketing authorisation application for the same product.

In the event of a serious disagreement among Member States, which makes it impossible for the Commission to decide, a decision may be taken by the Council of the European Union.
Information on medicinal products

Package leaflet, labelling and advertising

After Directive 65/65/EEC (still the foundation of Community pharmaceutical law), had been supplemented 10 years later by Directives 75/318/EEC\textsuperscript{12} and 75/319/EEC\textsuperscript{13} (mutual recognition), another decade was to elapse before the next historic milestone. This was the White Paper of June 1985, which set out a series of measures that were to extend Community law to various specific kinds of medicinal products, such as those derived from biotechnology, vaccines, toxins, serums and allergens, radiopharmaceutical products, products derived from human blood or plasma, and homeopathic medicines.

At the same time, Community lawmakers began turning their attention to pharmaceutical manufacturing and innovation as an economic activity. For example, Council Directive 89/105/EEC\textsuperscript{14} gives pharmaceutical companies assurances as to the transparency of the procedures used to control pharmaceutical prices, profits and reimbursement, whilst Regulation 1768/92\textsuperscript{15} allows patent life to be extended, so as to offset patent protection time taken up by marketing authorisation procedures.

To promote the appropriate use of medicines, the Council adopted four directives in 1992 on the wholesale distribution, classification for supply, labelling and package leaflets, and advertising of medicinal products for human use.

Directive 92/27/EEC\textsuperscript{16}, on labelling and package leaflets, benefits the consumer by requiring that all the information identifying the product be stated on the outer packaging. This information includes product name, pharmaceutical form, contents, name and address of authorisation holder, authorisation number and batch number, composition, excipients and method of administration, as well as certain important warnings. The labelling must be easily legible, clearly comprehensible and indelible. The language should be the one of the country where the product is placed on the market.

A package leaflet must now be included inside the packet unless all the information to be given in the leaflet is already conveyed on the outer or immediate packaging. Like the package leaflet, the labelling must be in the language(s) of the country where the product is marketed. The information must be clear and understandable for the patient. It should also state possible adverse effects, in accordance with the summary of product characteristics.

Directive 92/28/EEC\textsuperscript{17}, on advertising, distinguishes between medicines that are available over the counter, most of which may be advertised to the general public, and prescription-only ones, which may be advertised only to health professionals such as doctors, prescribers and pharmacists.

\textsuperscript{12} OJ N° L 147, 9/06/1975, p. 0001-0002
\textsuperscript{13} OJ N° L 147, 9/06/1975, p. 0013-0022
\textsuperscript{14} OJ N° L 040, 11/02/1989, p. 0008-0011
\textsuperscript{15} OJ N° L 182, 02/07/1992, p. 0001-0005
\textsuperscript{16} OJ N° L 113, 30/04/1992, p.008-0012
\textsuperscript{17} OJ N° L 113, 30/04/1992, p. 0013-0018
EU Member States are required to prohibit the advertising to the general public of medicinal products that are available on prescription only, or which contain psychotropic or narcotic substances. They may also prohibit such advertising where the product is eligible for reimbursement. The directive also lists a set of therapeutic indications that must not be mentioned in advertising to the general public.

The rules concerning the monitoring of advertising are modelled on those of the directive concerning misleading advertising. Hence, self-regulatory bodies play a major part as well as those people in pharmaceutical companies who are responsible for information relating to medicinal products and for the supervision of medical sales representatives.
Pharmacovigilance

Pharmacovigilance, or the surveillance of the safety of a medicinal product during its life on the market, is extensively regulated by EU directives and regulations. Council Regulation 2309/93 and Directive 75/319/EEC require Member States to establish national pharmacovigilance systems to collect and evaluate information on adverse reactions to medicinal products or their side effects and to take appropriate action where necessary. In addition, Commission regulation 540/95 lays down specific requirements for reporting non-serious unexpected adverse reactions.

When a medicinal product is first authorised, all the information available on it comes from experience in clinical trials - during which its potential risks are weighed with its potential benefits. Once it is placed on the market and used in a wider population, a lot more information on its benefits and risks becomes available. Pharmacovigilance systems are designed to collect and continuously evaluate this information. If a medicinal product's overall risk/benefit profile changes significantly for any reason, it may become necessary to vary, withdraw or suspend its use.

An EMEA Pharmacovigilance Working Party (reporting to the CPMP) provides a regulatory forum for Community-wide discussion and co-ordination of pharmacovigilance issues. All Member States also co-operate, via their national systems, with the World Health Organisation (WHO) Collaborating Centre for International Drug Monitoring.

Companies, too, must have pharmacovigilance systems in place, so that they can take appropriate action when necessary. Company-derived pharmacovigilance takes three forms: individual adverse reaction case reports, periodic safety update reports (PSURs), and company-sponsored post-authorisation safety studies.

Case reports and PSURs on nationally-authorised and mutually-recognised medicines are evaluated by national pharmacovigilance centres. In the case of nationally-authorised medicines, any action that the national centre deems necessary (e.g. varying, suspending or withdrawing the marketing authorisation), is notified to the EMEA and other Member States. For mutual recognition product PSURs, Member States have agreed that the Reference Member State will evaluate the information, identify any possible hazard and circulate its assessment to all Concerned Member States. PSURs on centrally-authorised products are evaluated by the rapporteur appointed by the CPMP.

In addition to the normal methods of collecting information on the use of a medicinal product, companies may also perform specific clinical studies to identify previously unrecognised risks or to confirm the safety of a medicinal product under marketed conditions. Adverse reactions observed during these studies are subject to the normal regulatory requirements and additional reports on the studies should be sent to the regulatory authorities to complete the safety information.

In the event of a suspected risk to public health, a company may notify urgent safety restrictions to the CPMP rapporteur (for centrally-authorised products), or the relevant competent authorities (for mutually-recognised ones) and immediately take action to
vary, withdraw or suspend the use of the medicinal product. Urgent safety restrictions for centralised products may also be initiated by the European Commission.

Furthermore, a Member State, the Commission or a company may refer a pharmacovigilance matter to the CPMP in cases where the interests of the Community are at stake, for example in the case of a potential serious public health risk from a medicinal product or where there are significant differences in approaches taken in Member States. The matter may then be referred to the Pharmacovigilance Working Party to provide scientific input, ultimately resulting in a CPMP opinion. The final decision that the Commission takes, on the CPMP's advice, is binding on all Member States where the product is marketed.

Adverse reaction reports on centrally-authorised products are entered in the "EudraWatch" database and monitored by the EMEA. EudraWatch is an integral part of the electronic communications network linking Member States, the Agency and the Commission.

Pharmacovigilance - Reporting procedure for Community-approved medicines
The EudraNet network links national authorities, the EMEA and the European Commission
EUDRA INFORMATION AND COMMUNICATION PROJECTS

The European Commission's Pharmaceutical Unit runs a variety of information and communication projects, collectively known as "Eudra" projects, which harness the latest electronic communications technology to further the European Commission's public health and single market policy aims.

Some of these projects are designed to facilitate the Commission's co-operation with the EMEA and national authorities responsible for human and veterinary medicines, and thus receive funding from the Community Interchange of Data between Administrations (IDA) programme. Others are designed to improve the flow of information to the pharmaceutical industry and the general public. The key Eudra projects are outlined below.
* EUDRANET - electronic network

The European Union Drug Regulatory Network (EudraNet), is an electronic communications system that allows Member State authorities to exchange information rapidly with the EMEA and the European Commission. Rapid and reliable communication, as well as mutual trust among all the parties involved, is essential to the efficient operation of the new pharmaceutical marketing authorisation system and pharmacovigilance. In the future, EudraNet may also become an equally useful means of communication with the authorities in European Free Trade Association (EFTA) and central and eastern European countries (CEECs).

* EUDRATRACK - mutual recognition of marketing authorisations

The EudraTrack workflow application which helps Member States to keep track of mutual recognition procedure applications, also benefits from EudraNet communication services.

* EUDRAWATCH - pharmacovigilance

The EudraWatch service for the electronic transmission and management of pharmacovigilance reports was established, in parallel with the EudraNet network, to meet the pharmacovigilance and information exchange requirements of the new marketing authorisation system. Under this system, pharmacovigilance data becomes an integral part of the marketing authorisation dossier, and must be updated with any application to renew the authorisation. To facilitate communication among regulators, and between regulators and industry, content and format specifications for EudraWatch pharmacovigilance reports are laid down in International Conference on Harmonisation (ICH) guidelines on "Data elements for the transmission of individual case safety reports" and ICH recommendations on electronic message formats.

* EUDRALEX - Community legislation

The Pharmaceutical Unit makes Community pharmaceutical legislation, guidelines, the Notice to Applicants and other relevant Community texts available on the web server18.

A Eudralex CD-ROM, which will enable users to link up directly to the web site and to keep track of legislative changes, should be available early in the new millennium.

WEBSITES

The Pharmaceutical Unit web site (http://pharmacos.eudra.org) provides access to practical information (such as the Community register of medicinal products, membership and meeting dates of Commission committees on human and veterinary

18 see list in annex 3
medicines, etc), as well as to draft pharmaceutical legislation and policy documents (e.g. contributions to round table discussions on completing the single pharmaceutical market). It is also a gateway to Eudralex.

The European Commission's EUROPA server (http://europa.eu.int) provides access to press releases, gateways to various Commission departments, and links to the home pages of other institutions and EU satellite agencies.

The Official Journal of the European Communities can be viewed on http://europa.eu.int/eur-lex. EUR-Lex provides free access to the C and L series of the Official Journal for 20 days after publication, to the EU Treaties (both consolidated and undergoing the ratification process), to EU legislation in force (including consolidated versions), and to recent judgments of the Court of Justice.
International relations and harmonisation processes

International Conference on Harmonisation (ICH)

Technical requirements for demonstrating the quality, safety and efficacy of new medicines have been almost fully harmonised throughout the European Union, United States and Japan, via the International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH).

ICH was launched in 1990 as a joint regulatory/industry project to make new pharmaceutical development and registration processes more efficient, in the interests of patients, public health, and cost-effectiveness, e.g. by preventing unnecessary duplication of clinical trials in humans and minimising animal testing.

By the end of the first phase of ICH activity, which ended at the fourth conference (ICH 4, Brussels, July 1997), tripartite guidelines had been finalised on 45 harmonisation topics, in four broad categories:

- "Quality" topics, which relate to chemical and pharmaceutical quality assurance (e.g. stability testing and impurity testing);

- "Safety" topics, which relate to in-vitro and in-vivo pre-clinical studies (e.g. carcinogenicity testing and genotoxicity testing);

- "Efficacy" topics, which relate to clinical studies in human subjects (e.g. dose response studies and good clinical practice);

- "Multidisciplinary" topics, i.e. those that do not fit uniquely into any of the above categories (e.g. medical terminology and electronic standards for the transmission of regulatory information).

As more and more testing requirements were harmonised by ICH guidelines, discussion turned the feasibility of developing a common format or Common Technical Document (CTD), for submitting this data to the regulatory authorities in all three ICH regions. The CTD has since been made a multidisciplinary topic, thus becoming an ICH project in its own right. It should be completed in time for the ICH 5 meeting (San Diego, November 2000).

At ICH 4, it was agreed that the second phase of ICH activity should ensure that:

- there is a mechanism to harmonise new technical requirements resulting from scientific progress and developments in innovative drug research;

- there is a process for updating and supplementing the current ICH guidelines when necessary and monitoring their use (to protect the benefits of harmonisation already achieved);

- future disharmony is prevented, through early collaboration and exchange of information on issues emerging in any of the three regions.
A useful spinoff of ICH work, the ICH Medical Dictionary for Regulatory Activities (MedDRA) Terminology, in English and Japanese translations, is available to subscribers (E-mail: khuntley@bdm.com).

Further details of ICH work and achievements are available on the ICH web site at http://www.ifpma.org/ich1.html.

**VICH**

ICH successes in harmonising regulatory requirements for human medicines inspired the launch, in 1996, of a similar harmonisation drive for veterinary medicines, known as "International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), under the auspices of the International Office of Epizootics (OIE). Besides the EU, Japan and USA, VICH includes Australia and New Zealand, as observers.

The VICH programme, which encompasses both pharmaceutical and biological veterinary medicines, is designed to harmonise regulatory standards, minimise their impact on trade, and meet consumer and political expectations of increased rigour in the protection of animal and human health, welfare and the environment. It aims to:

- implement harmonised guidelines for all registration requirements where significant differences exist among VICH members;

- proactively respond to emerging issues and science that impact on authorisation and supervision requirements within the VICH regions and/or adopted VICH guidelines;

- develop consultation and communication mechanisms that result in wider international acceptance of VICH guidelines.

By the time of its first major public conference (Brussels, November 1999), VICH was close to finalising 14 guidelines on quality and efficacy topics, and was about to release several draft biological quality monitoring and pharmacovigilance guidelines for consultation.

Further details of VICH work and achievements are available on the VICH web site at http://vich/eudra.org.
Central and eastern European countries (CEECs)

A key task of the Pharmaceutical Unit is to help pharmaceutical registration authorities in central and eastern European countries (CEECs19) and Cyprus to prepare for EU membership. For CEECs, preparing to join the Union entails not just incorporating EU legislation (the "acquis communautaire") in their national laws, but also adapting their administrative machinery and societies to make the acquis work.

Adapting to the acquis is a complex process, especially in heavily-regulated sectors like pharmaceuticals. Creating or upgrading regulatory institutions and structures often entails making radical changes in the responsibilities of civil servants, judges, and emerging private companies. The Pharmaceutical Unit assists CEECs in this task by arranging and concentrating technical support where it is most needed, so as to make the most of scarce resources. In doing so, it draws on expertise in the Union's own institutions, Member States and the private sector. The specialised assistance provided includes advice from legal and technical experts on how to interpret the acquis and draft national laws, information on implementation and enforcement mechanisms in the Member States, exchange programmes for regulators and access to administrative, language and specialised technical training.

But necessary as they are, institution-building and incorporating the acquis inevitably take time. CEEC patients in dire need of western medicines cannot wait while their societies adjust to the fine detail of the acquis. To their credit, CEEC regulatory drug authorities have addressed this need, by introducing a common simplified procedure for authorising the use on their territory of Community-authorised medicines. This procedure, established further to Collaboration Agreement of Drug Regulatory Authorities of European Union Associated Countries (CADREAC20), came into operation on 1 January 1999. The procedure is optional, and is initiated at the request of the marketing authorisation holder in the EU.

To assist CEEC institution-building and adjustment to the acquis, the European Commission has set up a pharmaceutical "Pan-Regulatory Forum" (PERF) of EU and CEEC officials, consumers and health professionals. This forum, initially designed to run for one year from June 1999, focuses on six priority action areas including pharmacovigilance, assessment of regulatory dossiers, good manufacturing practice (GMP) and practical implementation issues. The EMEA has been contracted to administer and provide the executive secretariat for this forum. It brings together CEEC and EU regulators in working groups and training sessions with the aim of designing to design mechanisms for adopting common technical requirements, ensuring EU legislation is properly enforced and identifying areas for further work. It is open to all partner countries21 in the EU’s "Phare" programme for CEECs (institution-building and investment support in candidate countries, supporting transition to democracy and market economy in non-candidate ones).

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19 The EU accession candidate countries are Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia and Slovenia, plus Cyprus.
21 PHARE members (autumn 1999): CADREAC members, plus non-candidates Albania, Former Yugoslav Republic of Macedonia (FYROM), and Bosnia and Herzegovina.
Meanwhile, to help eliminate technical barriers to pharmaceutical trade with the CEECs, the Commission is also negotiating protocols to a European conformity assessment agreements (PECAAs), to permit mutual recognition (e.g. of good manufacturing practice compliance) for medicinal products that used to need technical approval from both the importing and exporting countries. By autumn 1999, PECAAs were close to being signed with Hungary and the Czech Republic.

**Mutual recognition agreements**

Like PECAAs, Mutual Recognition Agreements (MRAs) facilitate trade, by eliminating the need to check, twice, that an imported medicinal product conforms to technical requirements - once in the exporting country, and once in the importing country. MRAs work on the basis of determining the equivalence of the two parties' regulatory requirements. Once equivalence has been determined, either party should be able to recognise the other party's assessment, so that, for example in the case of GMP inspections, one inspection will satisfy both internal and export requirements.

However, MRAs differ from PECAAs in that they are not, strictly speaking, harmonisation measures. Whereas, under PECAAs, candidate countries adopt exactly the same standards as EU Member States, MRAs allow standards to differ between parties, provided that each recognises the other's standards. MRAs may nonetheless facilitate subsequent harmonisation, as mutual recognition builds mutual confidence - a process that is accelerated by international harmonisation drives such as ICH.

For pharmaceutical companies, the expense, time and administrative complications of obtaining approvals abroad can be reduced by having a medicine evaluated in the country of manufacture, and by having compliance with good manufacturing practice (GMP) requirements certified by inspectors in that country. For pharmaceutical surveillance authorities, having another party's GMP inspectors certify GMP compliance in the country of manufacture saves the expense of sending their own GMP inspectors there to do the same job. For patients, these time and manpower savings in turn ensure faster, cheaper access to a wider range of medicines.

By autumn 1999, the EU had signed MRAs on pharmaceutical GMP with the USA, Canada, Australia and New Zealand, and was negotiating similar ones with Switzerland and Japan. Commission efforts will henceforth concentrate on the implementation of these agreements, on removing remaining trade barriers, and on improving access to emerging markets in Asia and Latin America.

**European Pharmacopoeia**

As long ago as the early 1960s, determination to reap the public health benefits of ensuring the free movement of medicines, within the Community, throughout Europe, and internationally, prompted European pharmaceutical policy-makers to seek ways to harmonise manufacturing and control standards, so as to eliminate technical barriers to trade.
The European Pharmacopoeia (http://www.pheur.org) was founded by Belgium, France, Germany, Italy, Luxembourg, Netherlands, Switzerland, and the UK in 1964 under a Council of Europe Convention, to help standardise their national pharmacopoeias (quality specifications for pharmaceutical preparations and their ingredients).

By autumn 1999, the Pharmacopoeia had 26 signatories (15 EU Member States, the European Community as such and 10 others\(^{22}\)), in which its monographs (quality specifications) have force of law, replacing the old national pharmacopoeias. Council Directive 75/318/EEC requires EU pharmaceutical manufacturers to use these monographs when compiling marketing authorisation applications.

The Pharmacopoeia also supplies manufacturers with "reference substances", which enable them to check the quality and conformity of medicines produced and marketed in Europe, or exported from it. It is now recognised as one of the main authorities on pharmaceutical quality and safety, and its co-operation with the European Union has resulted in the setting up of a scientific research programme to standardise biological medicines, and an official network of national medicine control laboratories (OMCLs). This pooling of expertise helps ensure that the same quality standards are guaranteed throughout Europe.

The Pharmacopoeia's European Department for the Quality of Medicines (EDQM) regularly attends meetings of European Commission and EMEA human and veterinary medicines committees in an observer capacity, and Commission and EMEA officials likewise attend sessions of the European Pharmacopoeia Commission.

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\(^{22}\) Bosnia, Croatia, Cyprus, Iceland, Norway, Slovakia, Slovenia, Switzerland, Former Yugoslav Republic of Macedonia (FYROM) and Turkey.
Industrial policy

The mission of the European Commission's Enterprise Directorate-General is to promote a business environment in which all European enterprises - including pharmaceutical companies - can fully realise their potential as an engine of economic growth and job creation in the European Union.

The policy measures that the Commission uses to accomplish this mission include promoting access to venture capital (especially for start-up companies), helping to provide better links between basic and applied research\(^{23}\), and negotiating to remove barriers to entering markets beyond the EU.

However, the task of ensuring that the European Union provides a firm base for innovation and industrial development is complicated, in the case of the pharmaceutical industry, by the unusual nature of its products. Medicinal products are viewed not just as industrial goods, but as a tool of public health policy. Responsibility for funding, managing and organising public health care systems - including pharmaceutical procurement - rests solely with individual EU Member States. This restricts the range of possible EU industrial policy measures to those on which all can agree, or which pursue aims they have already agreed on in principle - such as ensuring the free movement of medicines throughout the Community.

Industrial policy measures for the pharmaceutical industry must therefore be framed to ensure on the one hand that appropriate incentives are available for innovation and industrial growth, and on the other that patients have access to the pharmaceuticals they need, at an affordable cost. Striking an appropriate balance between industrial, medical and budgetary needs is a complex problem, to which there is no easy answer.

Answers have long been sought within the Commission's sphere of competence, and several of the key needs identified in its 1994 Communication on the Outlines of an Industrial Policy for the Pharmaceutical Sector in the European Community (COM(93)718 final) have since been met:

- the new Community marketing authorisation procedures are giving pharmaceutical innovators faster access to a wider market, and at the same time giving patients faster access to a wider range of innovative pharmaceuticals;

- European Parliament and Council Directive 98/44/EC\(^ {24}\), on the legal protection of biotechnological inventions, offers biopharmaceutical inventors the prospect of patent protection throughout the Union, and patients that of cures for hitherto untreatable diseases;

- breakthroughs have been achieved in facilitating access to third country markets with the conclusion of the first phase of ICH and the signing of mutual recognition agreements with the USA, Canada, Australia and New Zealand.

\(^{23}\) For example, through the EU's Fifth Framework Programme of Research, Development and Demonstration activities - http://europa.eu.int/comm/dg12/lp5.html).

\(^{24}\) OJ L213, 30/07/1998 p. 0013 - 0021
**Single market round tables**

Ideas as to how best to complete this single market for pharmaceuticals - without encroaching upon Member States' health policy prerogatives - have been debated at length by Commission, Member State and industry representatives at and between three annual round tables, beginning in 1996.

Measures have been suggested to enhance market transparency, competition, and patient empowerment, without compromising patients' access to medicines at affordable cost or the Member States' ability to meet public expenditure objectives. These measures are described in a Commission Communication on the Single Market in Pharmaceuticals (COM(98)588 final), which, together with other round table contributions, is available on [http://pharmacos.eudra.org/frankf/index.htm](http://pharmacos.eudra.org/frankf/index.htm).

**Pharmaceutical industry indicators**

The pharmaceutical industry in Europe is a strong industrial sector which makes a significant contribution to Europe's industrial base. In 1997, the European Union pharmaceutical trade surplus was Euro 10,500 million, and over Euro 10,000 million was spent on pharmaceutical R&D within the Union - a threefold increase over the previous ten years. Over Euro 87,000 million worth of products left factories in the EU in 1997, representing some 40% of global production.

The market value (at ex-factory prices) of the EU pharmaceutical market is just over Euro 62,000 million (just under 30% of the world market); its retail value now exceeds Euro 90,000 million, Euro 56,000 million of which is accounted for by payments by health care systems. In 1997, the pharmaceutical industry employed some 487,000 people within the EU, including 71,000 in R&D. In addition to a substantial R&D-based sector, the pharmaceutical industry in Europe also has active sectors dealing in generic (i.e. patent-expired) and OTC medicines.

Nevertheless, there are concerns, particularly in the global context in which this industry operates. The Commission's 1994 *Communication on the Outlines of an Industrial Policy for the Pharmaceutical Sector in the European Community* (COM(93)718 final) expressed concerns that the competitiveness of the European industry appears to be weakening: 20 years ago Europe led the way in pharmaceutical R&D; more recently, to judge from patent filings at least, Europe has been overtaken by the US. The trend identified in the 1994 Communication has been confirmed by the latest data. Of the 47 new active substances launched on the world market in 1997, 19 (or 40%), had been discovered and developed in Europe; 30 years ago, Europe's share of pharmaceutical discoveries was 65%.

On the biotechnology side, Europe has made a particularly poor start compared with progress in the USA, as was noted in the 1994 Communication. Figures compiled in 1995 on the invention and marketing of biotechnology-derived new active substances put the US share at 76%, Japan's at 14% and Europe's at 10%. There are however welcome signs that this is starting to change. Data based on a total of 770
biotechnology-derived medicines (including 206 genetically engineered ones) under development at the end of 1995 indicate that 25% of the biopharmaceutical development work is currently located in Europe (63% in the US, 7% in Japan): in gene therapy specifically, 22% of the development work is located in Europe (70% in the US, 1% in Japan).

Annexe 1

<table>
<thead>
<tr>
<th>Country</th>
<th>Total employment (units)</th>
<th>Employment in research (units)</th>
<th>Investment in research (ECU million)</th>
<th>Market value at ex-factory prices (ECU million)</th>
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<td>413</td>
<td>2 197</td>
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<td>4 045</td>
<td>361</td>
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<td>2 700</td>
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<td>260</td>
<td>5 305</td>
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<td>14 900</td>
<td>2 150</td>
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<td>n.a.</td>
<td>1 196</td>
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<td>1 173</td>
<td>81</td>
<td>1 118</td>
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<tr>
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</tr>
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</table>


Source: EFPIA, PhRMA, JPMA
Evolution of employment in the pharmaceutical sector (1986-1996)
Anannexe 3

Volume 1- Pharmaceutical legislation
Medicinal Products for Human Use

Volume 2A- Notice to Applicants
Medicinal products for Human Use Procedures for marketing authorisation

Volume 2B- Notice to Applicants
Medicinal Products for Human Use. Presentation and content of the dossier

Volume 3B- Guidelines
Medicinal Products for human use Quality and Biotechnology

Volume 3C-Guidelines
Medicinal Products for Human use. Efficacy

Volume 4-Pharmaceutical legislation
Medicinal products for human and veterinary use. Good Manufacturing Practises

Volume 5- Pharmaceutical Legislation
Veterinary medicinal products

Volume 6A- Notice to Applicants
Veterinary medicinal products
Procedures for marketing authorisation

Volume 6B- Notice to Applicants
Veterinary medicinal products
Presentation and content of the dossier

Volume 7- Guidelines
Veterinary medicinal products

Volume 8- Maximum Residue Limits
Veterinary medicinal products (IN PRODUCTION)
Content of dossier and residue evaluation
Summary reports

Volume 9- Pharmacovigilance
Medicinal Products for human use (IN PRODUCTION)
And veterinary use
Useful addresses

AESGP
Association Européenne des Spécialités Pharmaceutiques Grand Public-The European Proprietary Medicines Manufacturers’s Association)
7 Avenue de Tervuren
B- 1040 Brussels

EFPIA
European Federation of Pharmaceutical Industries and Associations
250 Avenue Louise
B - 1050 Brussels

EGA
European Generics Association
66 Avenue de Cortenbergh, PO BOX 193
B-1000 Brussels

EMEA
The European Agency for the Evaluation of Medicinal Products
7 Westferry Circus
Canary Wharf
London E14 4HB, UK

http://www.eudra2.emea.org

Useful Internet websites

EUROPA - The Web Service of the European Commission
http://europa.eu.int
EU Agencies Web Site
http://heads.medagencies.org/
IDA - The Committees managed by DG III/E/3 and their Working Parties:
http://www.ispo.cec.be/idaiida.html
ISPO - The EC Information Society Project Office
http://www.ispo.cec.be/
CORDIS - Community Research and Development Information Service
http://www.cordis.lu/
EUR-OP - The EC's Publications Office
http://eur-op.eu.int/
JRC - Joint Research Centre
http://www.jrc.org/jrc/